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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/815,730 | 04/02/2004 | James L. Hartley | IVGN 192.3 CON 2 | 1581 |

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| EXAMINER | |
|---|---|
| VOGEL, NANCY S | |
| **ART UNIT** | **PAPER NUMBER** |
| 1636 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/815,730 | HARTLEY ET AL. | |
| | Examiner | Art Unit | |
| | Nancy T. Vogel | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *19-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/31/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/07 has been entered.

Claims 19-37 are pending in the case.

Receipt of the Information Disclosure Statement on 10/31/07 is acknowledged.

Any rejection of record in the previous action not addressed in this office action is withdrawn.

### *Priority*

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the

requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 09/432,085, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The prior application does not disclose the method in which a negative selection marker and an antibiotic selection marker between a third and fourth recombination sited on a vector, with which an amplification production comprising a first and second recombination site is to be recombined. Priority date of 10/24/1997 is therefore utilized.

This is maintained for essentially the reasons of record.

Applicant has pointed to a section in the specification which discusses toxic genes that may be used as negative selection markers, and Figures 7C and 9B of the '085 application. However, these sections do not disclosure the method as recited in claim 19, which recites and utilizes the vector comprising the negative selection marker and an antibiotic resistance gene between a third recombination site and a fourth recombination site, which do not recombine with each other.

***Claim Rejections - 35 USC § 103***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 19-30, 32-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson et al. (WO93/ Johnson et al. (WO93/19172) (AO3, cited by applicants) in view of Bernard (Biotechniques 21(2):320-323).

This rejection is maintained essentially for the reasons set forth in the previous Office action mailed, 7/13/07. To recapitulate:

Johnson et al. disclose a method of cloning an amplification product comprising obtaining an amplification product comprising a first recombination site and a second recombination site which do not recombine with each other; and combining said product with a vector comprising a third recombination site and a fourth recombination site which do not recombine with each other, under conditions such that recombination occurs between said first and third and second and fourth recombination sites, thereby producing a product vector (see pages 21-23). At page 22, line 31 – page 23, line 12, it is disclosed that different site specific recombination sites may be used in the first vector, as well as in the second vector, such that there will not be recombination between said sites within each vector, but that each vector has a recombination site that recombines with a site on the other vector. The reference discloses that the method may be carried out in vitro (see page 21, lines 9-11; see claims). The reference discloses that the first site may be the loxP site, and the second may be the loxP 511 site (page 23, lines 13-22) or attB, attP, attL, attR. The recombinase protein may be Cre, Int, IHF (see pages 29-33). The reference discloses that the vector is an expression vector comprising promoter, origin of replication, selectable marker, and genes (see page 20-23). Johnson et al. disclose the use of markers on the plasmids

which are being subject to site specific recombination for the purpose of selection of desirable outcomes (see Figures).

The difference between the reference and the claims is that a negative selection marker and an antibiotic resistance gene are present on the vector.

However, the use of antibiotic resistance and negative selection markers on plasmids is well known in the art, as taught by Bernard (Biotechniques 21(2):320-323). Bernard et al. teach the use of a negative selective marker such as ccdB for selection of desired DNA molecules.

It would have been obvious to one of ordinary skill in the art to have utilized antibiotic resistance genes and negative selection markers such as ccdB in the recombination process of Johnson et al., since it was well known in the art to include such selection markers in DNA molecules in order to select for the presence or absence of a DNA molecule of interest, as taught by Bernard. One would have been motivated to do so by the desire to increase the ability to select for a DNA molecule of interest.

Applicant's arguments filed 10/31/07 have been considered, but have not been found convincing.

Applicants have argued that Bernard et al. "describes a selection vector and associated system which involves the insertion of nucleic acid into the vector at a site which encodes a toxic fusion protein. This insertion results in insertional inactivation of the toxic fusion protein coding region" 9pages 6-7). Applicant then summarizes Figure 1 of the captioned application, by which it is assumed is intended the instant application (page 7). Applicant then states that "none of the art cited by the Examiner would lead

one skilled in the art to methods defined by the pending claims" (page 7). However, there arguments presented to support this conclusion. It is maintained that the previous Office action set forth adequate reasoning as to why one would have been Motivated to combine the teachings of the references, and why the references, when considered in combination, rendered the invention obvious to one of ordinary skill in the art. Therefore, the rejection is maintained.

Claims 19-30, 32-37 are rejected under 35 U.S.C. 102(e) as being anticipated by Griffiths et al. (US Patent No. 5,962,255) in view of Bernard (Biotechniques 21(2):320-323)

This rejection is maintained essentially for the reasons set forth in the previous office action, mailed 7/13/07.

To recapitulate:

Griffiths et al teach a method for cloning an amplified linear nucleic acid by amplifying a nucleic acid template with a first primer comprising a first recombination site and second primer comprising a second recombination site, where the first and second recombination sites do not recombine with each other. The vector comprises third and fourth recombination sites which will recombine with the first and second recombination sites, as recited in the instant claim 1 (see Griffiths at Example 6-7, see claims). Recombining the amplified nucleic acid and a vector in the presence of a recombination protein produces a recombined vector (product vector). The

amplification is accomplished by an amplification reaction, which may be via replication in a host cell. The recombined (product) vector is expressed in a host cell. The vector comprises a promoter, a restriction site, an origin of replication, a cloning site and a gene. The product nucleic acid is linear. The first, second, third or fourth recombination sites are lox sites or mutants thereof (loxP and loxP511). The recombination sites may be lox or att sites (see Griffiths et al, column 19 and Example 6 and claims). The product nucleic acid molecule and said vector are combined in the presence of at least one recombination protein. The recombinase may be Cre or other recombinases (see col. 19 and 23).

The difference between the reference and the claims is that a negative selection marker and an antibiotic resistance gene are present on the vector.

However, the use of antibiotic resistance and negative selection markers on plasmids is well known in the art, as taught by Bernard (Biotechniques 21(2):320-323). Bernard et al. teach the use of a negative selective marker such as ccdB for selection of desired DNA molecules.

It would have been obvious to one of ordinary skill in the art to have utilized antibiotic resistance genes and negative selection markers such as ccdB in the recombination process of Johnson et al., since it was well known in the art to include such selection markers in DNA molecules in order to select for the presence or absence of a DNA molecule of interest, as taught by Bernard. One would have been motivated to do so by the desire to increase the ability to select for a DNA molecule of interest.

Applicant's arguments filed 10/31/07 have been considered, but have not been found convincing. Applicants have set forth the same argument for this rejection as set forth in response to the above rejection over Johnson in view of Bernard et al. For the reasons set forth above, the arguments are not found convincing and the rejection is maintained.

The following is a new rejection:

Claims 19-30, 32-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson et al. (WO93/ Johnson et al. (WO93/19172) (AO3, cited by applicants) in view of Bernard (US Patent 5,910,438).

Johnson et al. disclose a method of cloning an amplification product comprising obtaining an amplification product comprising a first recombination site and a second recombination site which do not recombine with each other; and combining said product with a vector comprising a third recombination site and a fourth recombination site which do not recombine with each other, under conditions such that recombination occurs between said first and third and second and fourth recombination sites, thereby producing a product vector (see pages 21-23). At page 22, line 31 – page 23, line 12, it is disclosed that different site specific recombination sites may be used in the first vector, as well as in the second vector, such that there will not be recombination between said sites within each vector, but that each vector has a recombination site that recombines with a site on the other vector. The reference discloses that the method may be carried out in vitro (see page 21, lines 9-11; see claims). The reference

discloses that the first site may be the loxP site, and the second may be the loxP 511 site (page 23, lines 13-22) or attB, attP, attL, attR. The recombinase protein may be Cre, Int, IHF (see pages 29-33). The reference discloses that the vector is an expression vector comprising promoter, origin of replication, selectable marker, and genes (see page 20-23). Johnson et al. disclose the use of markers on the plasmids which are being subject to site specific recombination for the purpose of selection of desirable outcomes (see Figures).

The difference between the reference and the claims is that a negative selection marker and an antibiotic resistance gene are present on the vector.

However, the use of antibiotic resistance and negative selection markers on plasmids is well known in the art, as taught by Bernard et al. (US Patent 5,910,438). Bernard et al. teach the use of a negative selective marker such as ccdB for selection of desired DNA molecules (see cols. 3-4).

It would have been obvious to one of ordinary skill in the art to have utilized antibiotic resistance genes and negative selection markers such as ccdB in the recombination process of Johnson et al., since it was well known in the art to include such selection markers in DNA molecules in order to select for the presence or absence of a DNA molecule of interest, as taught by Bernard. One would have been motivated to do so by the desire to increase the ability to select for a DNA molecule of interest.

Claims 19-30, 32-37 are rejected under 35 U.S.C. 102(e) as being anticipated by Griffiths et al. (US Patent No. 5,962,255) in view of Bernard (US Patent 5,910,438).

Griffiths et al teach a method for cloning an amplified linear nucleic acid by amplifying a nucleic acid template with a first primer comprising a first recombination site and second primer comprising a second recombination site, where the first and second recombination sites do not recombine with each other. The vector comprises third and fourth recombination sites which will recombine with the first and second recombination sites, as recited in the instant claim 1 (see Griffiths at Example 6-7, see claims). Recombining the amplified nucleic acid and a vector in the presence of a recombination protein produces a recombined vector (product vector). The amplification is accomplished by an amplification reaction, which may be via replication in a host cell. The recombined (product) vector is expressed in a host cell. The vector comprises a promoter, a restriction site, an origin of replication, a cloning site and a gene. The product nucleic acid is linear. The first, second, third or fourth recombination sites are lox sites or mutants thereof (loxP and loxP511). The recombination sites may be lox or att sites (see Griffiths et al, column 19 and Example 6 and claims). The product nucleic acid molecule and said vector are combined in the presence of at least one recombination protein. The recombinase may be Cre or other recombinases (see col. 19 and 23).

The difference between the reference and the claims is that a negative selection marker and an antibiotic resistance gene are present on the vector.

However, the use of antibiotic resistance and negative selection markers on plasmids is well known in the art, as taught by Bernard (US Patent 5,910,438). Bernard

et al. teach the use of a negative selective marker such as ccdB for selection of desired DNA molecules (see cols. 3-4).

It would have been obvious to one of ordinary skill in the art to have utilized antibiotic resistance genes and negative selection markers such as ccdB in the recombination process of Johnson et al., since it was well known in the art to include such selection markers in DNA molecules in order to select for the presence or absence of a DNA molecule of interest, as taught by Bernard. One would have been motivated to do so by the desire to increase the ability to select for a DNA molecule of interest.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 19, 22-37 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 29-34, of U.S. Patent No. 5,888,732.

This rejection is maintained essentially for the reasons made of record in the previous Office action. Applicants have stated in the arguments filed 10/31/07 that they wish to defer responding to the rejection until allowable subject matter is determined. Therefore the rejection is maintained.

Claims 19-37 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 15-20 and 45-55 of U.S. Patent No. 6720140.

This rejection is maintained essentially for the reasons made of record in the previous Office action. Applicants have stated in the arguments filed 10/31/07 that they wish to defer responding to the rejection until allowable subject matter is determined. Therefore the rejection is maintained.

The following is a new rejection:

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 and by dependence claims 20-37 are vague and indefinite in the phrase "the third and fourth recombination sites do not recombine with each other" since it is not clear what molecules are encompassed by this phrase. It is known in the art that illegitimate (non-homologous) recombination may occur at some low frequency even between molecules with little or no homology, and therefore it is not clear what is intended by the phrase "do not recombine with each other", and intended metes and bounds of the claims cannot be determined.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy T. Vogel whose telephone number is (571) 272-0780. The examiner can normally be reached on 7:00 - 3:30, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NANCY VOGEL
PRIMARY EXAMINER

NV
1/18/08